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Laboratory adverse events and discontinuation of therapy according to CD4⁺ cell count at the start of antiretroviral therapy

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Objective: Few data describe antiretroviral treatment (ART)-related adverse events when treatment is initiated at CD4⁺ cell counts more than 350 cells/ μ l. We compared rates of laboratory-defined adverse events (LDAEs) according to CD4⁺ cell count at ART initiation.

Design: Analysis of on-going cohort study.

Methods: ART-naïve persons initiating ART from 2000 to 2010 were included. Chi-square, analysis of variance (ANOVA) and Kruskal–Wallis tests compared characteristics among those starting ART with a CD4⁺ cell count of 350 or less, 351–499 and at least 500 cells/ μ l. Time-updated Poisson regression compared rates of LDAE in the three CD4⁺ cell strata. Cox proportional hazard models compared risk of ART discontinuation.

Results: Nine thousand, four hundred and six individuals were included: median age 37 years, 61% white, 80% men, median viral load 4.8 log copies/ml. Four hundred and forty-seven (4.9%) and 1099 (11.7%) started ART with a CD4⁺ cell count at least 500 and 351–499 cells/ μ l, respectively. One thousand, two hundred and eighty-three (13.6%) patients experienced at least one LDAE. The rate of LDAE did not differ between those starting ART with a CD4⁺ cell count 351–499 and less than 350 cells/ μ l [relative rate 0.90, 95% confidence interval (CI) 0.74–1.09], but an increased risk of ART discontinuation was observed (hazard ratio 1.58, 95% CI 1.10–2.27). Those starting ART at CD4⁺ cell count at least 500 cells/ μ l had an increased rate of LDAE (relative rate 1.44, 95% CI 1.13–1.82) but were not more likely to discontinue ART (hazard ratio 1.15, 95% CI 0.64–2.09).

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Conclusion: This study demonstrates the need to consider ART-related toxicities when initiating therapy at CD4⁺ cell counts at least 500 cells/ μ l. Whilst evidence from randomized controlled trials is awaited, the timing of ART initiation in terms of benefits and risks of ART remains an important question.

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Introduction

The impact of antiretroviral therapy (ART) on viral transmission [1] and pragmatic programmatic recommendations have led to several HIV treatment guidelines committees now recommending ART at CD4⁺ cell counts more than 350 cells/ μ l [2–4]. Although public health benefits of earlier ART have recently been reported by the HPTN 052 study [1,5] and from observational studies within HIV endemic communities in Kwa-Zulu Natal [6], there remains insufficient randomized evidence on the risk:benefit ratio for the individual to support a shift to earlier ART initiation [7]. Currently, randomized controlled trial (RCT) evidence demonstrates a survival benefit of initiating ART at CD4⁺ cell count of 350 cells/ μ l or less compared with deferring to lower CD4⁺ cell count levels [8]. Well designed cohort studies have also shown morbidity and mortality benefits of ART at CD4⁺ cell counts more than 350 cells/ μ l with these effects appearing enhanced in the presence of comorbidities, coinfections and advancing age [9,10]. Other analyses, however, have not demonstrated clear survival benefits for asymptomatic HIV-positive individuals with CD4⁺ cell counts more than 500 cells/ μ l [11], and as such, possible survival benefits must be balanced against potential ART toxicities. It is hoped that the START and TEMPRANO trials (RCTs to investigate the risks and benefits to an individual of early ART initiation) will definitively address this particular question, but these will not report until 2015 [12,13]. In the meantime, data from observational cohorts provide valuable direction.

The UK Collaborative HIV Cohort (CHIC) Study is an observational study collecting data from many of the UK's largest HIV treatment centres [14]. We sought to determine the relative risk of developing severe (grade 3/4) [15] laboratory-defined adverse events (LDAEs) and rates of ART discontinuation among individuals with CD4⁺ cell counts of 350 or less, 351–499 and at least 500 cells/ μ l at ART initiation.

Materials and methods

Individuals were included in this study if they initiated ART between 2000 and 2010 at a UK CHIC centre that

provided laboratory data. Those excluded were pregnant women, those with a viral load less than 50 copies HIV RNA/ml at ART initiation and those without at least one CD4⁺ cell count, viral load or laboratory measurement during follow-up. Pregnancy was established through linkage between the UK CHIC and National Study of HIV in Pregnancy and Childhood (NSHPC) databases [16]. Eligible individuals were followed until the date last seen at a UK CHIC centre or the earliest of drop-out of follow-up for at least 18 months; discontinuation of ART for at least 1 month; transfer to a centre not providing laboratory data; pregnancy.

LDAEs were defined as grade 3/4 adverse events [15] for any of alanine transaminase (ALT); aspartate transaminase (AST); alkaline phosphatase (ALP); albumin; creatinine; haemoglobin; platelets; amylase; cholesterol; glucose. Bilirubin was not considered a LDAE so as to exclude atazanavir-induced hyperbilirubinaemia. ART discontinuation was defined as stopping all ART for at least 1 month.

Statistical analysis

Baseline characteristics according to CD4⁺ cell count at ART start were compared using Chi-square and analysis of variance (ANOVA) or Kruskal–Wallis tests. Poisson regression compared LDAE rates according to CD4⁺ cell count at ART initiation, censoring follow-up at first LDAE. In sensitivity analyses, we excluded those with hepatitis B virus (HBV) or hepatitis C virus (HCV) coinfection and those who commenced nevirapine at CD4⁺ cell counts more than 350 cells/ μ l, as this is now contraindicated [17]. Further Poisson regression models considered rates of LDAE that were likely to be related to liver (ALT, AST, ALP, albumin), kidney (creatinine), blood (haemoglobin, platelets) and other body systems (amylase, cholesterol, glucose) separately. Individuals' follow-up was split into 1-month intervals to create time-updated covariates for viral load, ART regimen, HBV/HCV status and time on ART. Time-independent covariates were sex, exposure category, ethnicity, age and previous experience of a LDAE at ART start. Time-updated Cox proportional hazards models investigated associations between CD4⁺ cell count and LDAE and the risk of discontinuing ART considering the same covariates as listed above as well as LDAE as a time-updated covariate. To avoid including those who

discontinued treatment at high CD4⁺ cell counts as part of the SPARTAC study [18], we first only considered discontinuations more than 1 year after the start of ART, excluding those who attended main recruiting centres for the SPARTAC study. In addition, the analysis was performed considering all discontinuations occurring after ART initiation (including those in the first year) but restricting to the few centres that had no involvement in the SPARTAC study. All analyses were performed in SAS (version 9.3; SAS Institute Inc., Cary, North Carolina, USA).

Results

A total of 14 022 individuals commenced ART after 2000 in a centre that provided laboratory data. Of these, 3068 were excluded with viral load less than 50 copies/ml at ART start, 534 had no follow-up, 363 had no CD4⁺ cell count, 432 were pregnant and 219 had no laboratory measures. Excluded individuals were more likely to be female, of black or unknown ethnicity, and less likely to have acquired HIV through sex between men.

Of 9406 patients, 7860 (83.6%), 1099 (11.7%) and 447 (4.8%) started ART with a CD4⁺ cell count of 350 or less, 351–499 and at least 500 cells/ μ l, respectively. Those who started therapy with a CD4⁺ cell count more than 350 cells/ μ l were more likely to be white men who acquired HIV through sex with men. HBV coinfection was observed in 5.8% of those with a CD4⁺ cell count at least 500 cells/ μ l compared with 2.6 and 3% in the 351–499 and 350 cells/ μ l or less groups, respectively ($P < 0.0001$), whilst HCV coinfection was found in 4.5, 6.1 and 4.0%, respectively. Initial ART regimens differed across CD4⁺ cell strata, with those in the at least 500 cells/ μ l group more likely to begin a protease inhibitor-based regimen ($P < 0.0001$) (Table 1).

Rates of laboratory-defined adverse events

In 27 861 person-years of follow up, 1283 (13.6%) individuals experienced a LDAE. There were 1094, 113 and 76 individuals with a LDAE in those starting ART with a CD4⁺ cell count of 350 or less, 351–499 and at least 500 cells/ μ l giving incidence rates [95% confidence interval (95% CI)] of 4.6 (4.4–4.7), 4.9 (4.0–5.8) and 8.2 (6.4–10.1) per 100 person-years, respectively. Those who started ART with a CD4⁺ cell count at least 500 cells/ μ l had a higher rate of LDAE in both unadjusted and adjusted analyses (relative rate, 95% CI 1.44, 1.13–1.82) than in those commencing ART below 350 cells/ μ l (Fig. 1a). No differences in rates of LDAE were seen between those starting ART at CD4⁺ cell count 351–499 or 350 cells/ μ l or less (relative rate, 95% CI 0.90 (0.74–1.09)). Excluding those with HBV/HCV coinfection or those who started a nevirapine regimen with a CD4⁺ cell count greater than 350 cells/ μ l did not alter our conclusions (results not shown).

Those with a CD4⁺ cell count at least 500 cells/ μ l had a greater risk of liver-related abnormalities after adjustment for other factors (relative rate, 95% CI 1.45, 1.03–2.04). There was no evidence of more liver, kidney, blood or other LDAEs in the 351–499 cells/ μ l CD4⁺ cell count group compared to the 350 cells/ μ l or less CD4⁺ cell count group, in either unadjusted or adjusted analyses (Fig. 1).

Discontinuation of antiretroviral therapy

Of 4583 individuals included in the analysis of ART discontinuation after 1 year, 15.2, 14.2 and 18.6% of the 350 or less, 351–499 and at least 500 cells/ μ l CD4⁺ cell count groups discontinued ART, respectively. Those excluded from this analysis were more likely to be of unknown ethnicity, to have started ART since 2008 and to have a CD4⁺ cell count greater than 350 cells/ μ l. Neither CD4⁺ cell count nor LDAEs were associated with discontinuation of ART after 1 year (results not shown).

In 1746 individuals attending centres not involved in the SPARTAC study, 27.8, 28.6 and 31.3% of those who started ART with a CD4⁺ cell count 350 or less, 351–499 and at least 500 cells/ μ l discontinued ART. After adjustment for viral load, ART regimen, centre and exposure group, an increased risk of discontinuation was seen in those initiating ART with a CD4⁺ cell count 351–499 cells/ μ l (hazard ratio, 95% CI 1.59, 1.11–2.29) but not in those with a CD4⁺ cell count at least 500 cells/ μ l (1.16, 0.64–2.09). LDAE was not associated with ART discontinuation (0.77, 0.54–1.10) and did not explain the increased risk of discontinuation in those initiating ART with a CD4⁺ cell count 351–499 cells/ μ l, as the CD4⁺ cell effect estimates remained unchanged with the inclusion of LDAE in the model (hazard ratio, 95% CI 1.58, 1.10–2.27 351–499 cells/ μ l; 1.15, 0.64–2.09 \geq 500 cells/ μ l).

Discussion

Individuals starting ART with a CD4⁺ cell count at least 500 cells/ μ l had a 44% increased risk of grade 3/4 LDAE compared with those initiating ART with a CD4⁺ cell count 350 cells/ μ l or less. This increased risk was largely explained by liver-test abnormalities. Higher rates of discontinuation were observed in those starting ART with a CD4⁺ cell count between 351 and 499 cells/ μ l in a small group of centres, but presence of a LDAE was not associated with ART discontinuation.

Despite adjusting for possible confounders, limitations persist in our analysis. Firstly, the indication for starting ART in those with a CD4⁺ cell count more than 350 cells/ μ l was not known. It is likely that many individuals starting ART with CD4⁺ cell counts at least 500 cells/ μ l did so due to the presence of comorbidities,

Table 1. Patient characteristics at start of antiretroviral therapy, stratified by CD4⁺ cell count at start of antiretroviral therapy.

	All	CD4 ⁺ cell count at start of ART (cells/ μ l)			<i>P</i>
		<350	351–499	>500	
<i>N</i>	9406	7860	1099	447	
Age, median (IQR) years	37 (32–43)	37 (32–43)	38 (32–44)	35 (30–42)	0.016 ^a
Sex, <i>n</i> (%)					
Male	7511 (79.9)	6147 (78.2)	958 (87.2)	406 (90.8)	<0.0001 ^b
Ethnicity, <i>n</i> (%)					
White	5707 (60.7)	4586 (58.4)	787 (71.6)	334 (74.7)	<0.0001 ^b
Black African	2034 (21.6)	1861 (23.7)	131 (11.9)	42 (9.4)	
Black other	473 (5.0)	404 (5.1)	52 (4.7)	17 (3.8)	
Other/unknown	1192 (12.7)	1009 (12.8)	129 (11.7)	54 (12.1)	
Mode of HIV acquisition, <i>n</i> (%)					
Homosexual/bisexual	5666 (60.2)	4518 (57.5)	801 (72.9)	347 (77.6)	<0.0001 ^b
Heterosexual	3019 (32.1)	2739 (34.9)	212 (19.3)	68 (15.2)	
Other/unknown	721 (7.7)	603 (7.7)	86 (7.8)	32 (7.2)	
Hepatitis B coinfection, <i>n</i> (%)					
No	5986 (63.6)	4913 (62.5)	775 (70.5)	298 (66.7)	<0.0001 ^b
Yes	290 (3.1)	235 (3.0)	29 (2.6)	26 (5.8)	
Not tested	3130 (33.3)	2712 (34.5)	295 (26.8)	123 (27.5)	
Hepatitis C coinfection, <i>n</i> (%)					
No	6209 (66.0)	5107 (65.0)	784 (71.3)	318 (71.1)	<0.0001 ^b
Yes	398 (4.2)	311 (4.0)	67 (6.1)	20 (4.5)	
Not tested	2799 (29.8)	2442 (31.1)	248 (22.6)	109 (24.4)	
Viral load, median (IQR) log ₁₀ copies/ml	4.8 (3.9–5.3)	4.8 (4.1–5.3)	4.4 (3.3–5.0)	4.3 (3.0–5.0)	<0.0001 ^c
Year of starting ART, <i>n</i> (%)					
2000–2003	2325 (24.7)	2035 (25.9)	160 (14.6)	130 (29.1)	<0.0001 ^b
2004–2007	3734 (39.7)	3257 (41.4)	339 (30.9)	138 (30.9)	
2008–2010	3347 (35.6)	2568 (32.7)	600 (54.6)	179 (40.0)	
Regimen type, <i>n</i> (%)					
2 NRTI and PI (/r)	2221 (23.7)	1752 (22.3)	295 (26.8)	174 (38.9)	<0.0001 ^b
2 NRTI and PI	169 (1.8)	141 (1.8)	16 (1.5)	12 (2.7)	
2 NRTI and NNRTI	6513 (69.2)	5559 (70.7)	718 (65.3)	236 (52.8)	
≥ 3 NRTI	203 (2.2)	173 (2.2)	22 (2.0)	8 (1.8)	
Other combination	300 (3.2)	235 (3.0)	48 (4.4)	17 (3.8)	
Previous adverse event					
Yes	825 (8.8)	679 (8.6)	98 (8.9)	48 (10.7)	0.31 ^b

ART, antiretroviral therapy; IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI (/r), protease inhibitor (with/without ritonavir). *P* = *p*-value of test of an overall difference between the 3 CD4⁺ cell count groups.

^aAnalysis of variance (ANOVA) test.

^bChi-square test.

^cKruskal–Wallis test.

which may independently cause laboratory abnormalities that would have been classified as LDEs in our analyses. Although we were unable to capture much information on the presence of comorbidities at ART initiation, we did observe higher rates of HBV coinfection in those with CD4⁺ cell counts at least 500 cells/ μ l; however, it must be acknowledged that information on coinfection with HBV or HCV was unavailable for a large proportion of people. Adjustment for HBV/HCV coinfection and LDE prior to ART initiation, to try and account for comorbidity, had no impact on the association between CD4⁺ cell count and LDE. A possible explanation for the increased rate of liver-related LDE is that HIV seroconverters may be overrepresented in the group initiating ART with a CD4⁺ cell count at least 500 cells/ μ l when elevated transaminases is common [19,20]. Exclusion of those who started a nevirapine-containing regimen at a CD4⁺ cell count more than 350 cells/ μ l did not alter our conclusions.

One concern of earlier ART initiation is the assumed ambivalence of asymptomatic HIV-positive individuals who start ART with high CD4⁺ cell counts who may be less inclined to remain adherent to ART in the long term. We saw no evidence that starting ART with a CD4⁺ cell count more than 350 cells/ μ l was associated with more treatment discontinuation after 1 year, but observed an increased risk of discontinuation at any time with a CD4⁺ cell count between 351 and 499 cells/ μ l in a small selection of centres. Reasons for ART discontinuation are not well reported in the UK CHIC study; however, this association did not appear to be explained by presence of an LDE. The occurrence of grade 3/4 LDEs was not independently associated with increased discontinuation rates, an observation in agreement with the recent publication of the UK Register of HIV Seroconverters [21].

ART guidelines may be moving towards universal treatment irrespective of CD4⁺ cell count. The

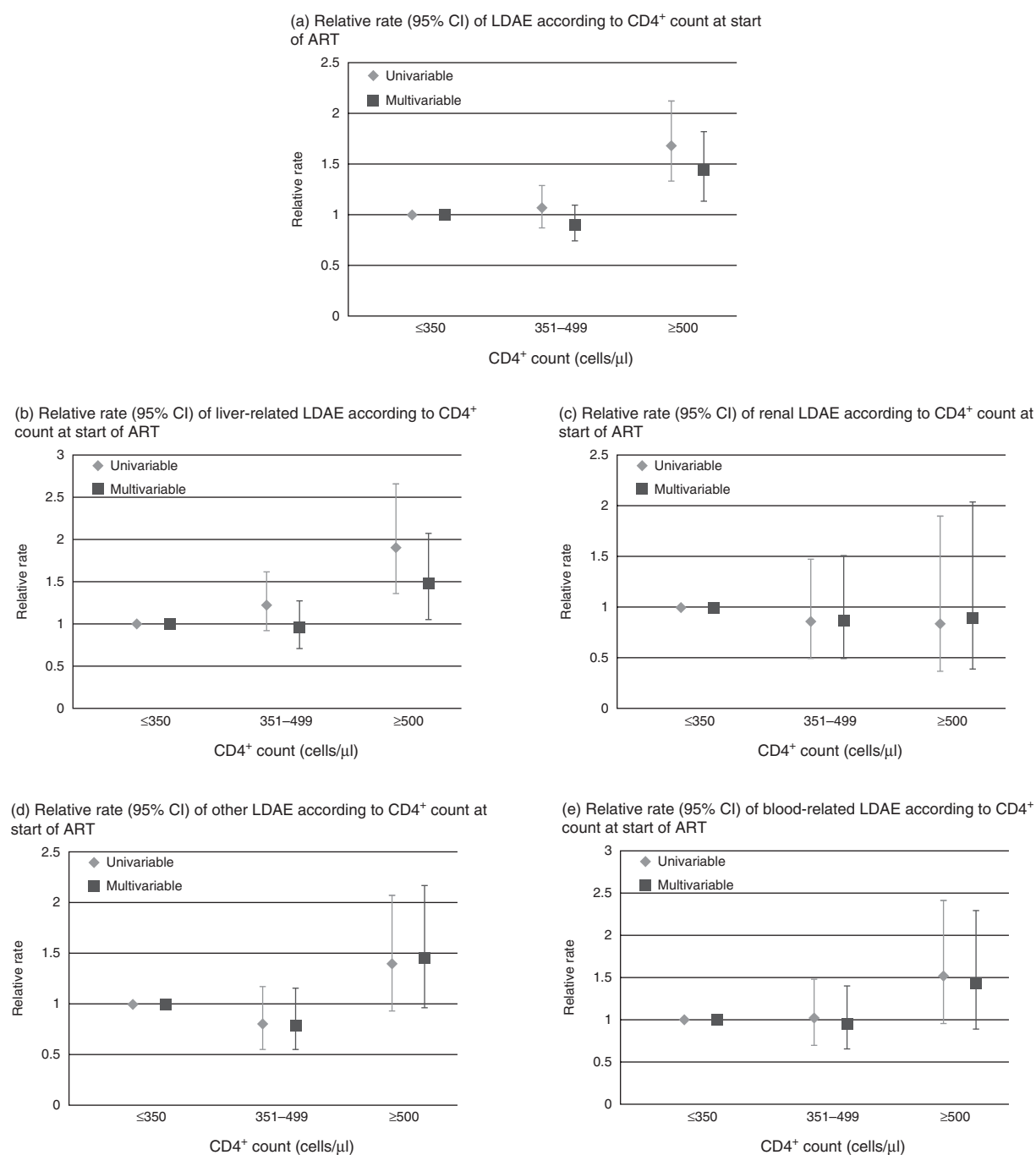


Fig. 1. Rate of laboratory-defined adverse events according to CD4⁺ cell count group at start of combination antiretroviral therapy. All univariable estimates adjusted for centre due to differences in testing practices. (a) Multivariable model adjusted for viral load, ART regimen, HBV coinfection, HCV coinfection, age, exposure, time on ART, centre. (b) Multivariable model adjusted for viral load, ART regimen, HBV coinfection, HCV coinfection, sex, ethnicity, time on ART, centre. (c) Multivariable model adjusted for viral load, antiretroviral regimen, ethnicity, age, centre. (d) Multivariable model adjusted for viral load, ART regimen, time on ART, exposure, age, centre. (e) Multivariable model adjusted for viral load, ART regimen, HBV coinfection, HCV coinfection, exposure, time on ART, centre. ART, antiretroviral therapy; CI, confidence interval; LDAE, laboratory-defined adverse event.

individual risk of ART-related adverse events must be evaluated in the context of the potential benefits for that individual, considering comorbidities, age, sexual practices and long-term prognosis. Although we await evidence from ongoing RCTs regarding

the potential risks and benefits of ART initiation with CD4⁺ cell counts at least 500 cells/μl, the potential for added adverse events in starting ART at high CD4⁺ cell counts must remain a key discussion with patients.

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S.J. performed the analysis and helped prepare the manuscript. C.A.S. and S.F. designed the study and were involved in analysis and preparation of the manuscript. K.Q. was involved in discussions around study design and analysis and helped prepare the manuscript. T.H. prepared

the data used for the study. As steering committee members for participating centres, P.H., F.A.P., R.G., M.N., M.G., M.F., M.J., D.C., C.L. advised on study concept and critically reviewed the analysis.

Conflicts of interest

S.J., T.H., K.Q. and C.L. have no conflicts of interest to declare. J.W. has received funds from Gilead sciences in connection with conference attendance. P.H. has received funding from Bristol Myers Squibb (BMS), Viiv, Gilead, Boehringer-Ingelheim, Merck and Johnson and Johnson in connection with conference attendance, speakers fees, consultancy, project grants and preparation of educational materials. M.F. has received funding from Gilead, BMS, Viiv, Abbott, Janssen and Merck in connection with project grants, speakers fees and conference attendance. FAP has received funding from BMS, Gilead, Viiv, Janssen in connection with speakers fees, project grants, conference attendance and preparation of educational materials. M.N. has received funding from Merck, Viiv, Gilead, Viiv and Abbott in connection with project grants, consultancy, speakers fees, conference attendance and preparation of educational materials. M.G. has received speakers fees from Janssen, BMS, Gilead, Viiv, Micropharma, CSL Behring. D.C. has received fees from BMS, Viiv and Gilead in connection with conference attendance and preparation of educational materials. R.G. has received funding from BMS, Gilead, Pfizer, Janssen, Roche and Merck in connection with project grants, conference attendance, speakers fees and membership of advisory boards. C.A.S. has received funding from Glaxo-Smith Klein, Janssen, Abbott, Gilead, BMS and Viiv in connection with speakers fees, membership of advisory boards and preparation of educational materials. S.F. has received grants from NIH, Gates, BRC and MRC. M.J. has received honoraria and research funding from VIIV Healthcare, Janssen-Cilag, Abbvie, Gilead Sciences, BMS and MSD.

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